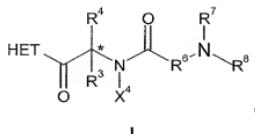


CLAIMS

1. A method for improving functional health status in a patient in need thereof which comprises administering to the patient a therapeutically effective amount of a growth hormone secretagogue.
- 5 2. A method of claim 1 wherein the instrumental activities of daily living of the patient are improved.
3. A method of claim 1 wherein the energy level of the patient is improved.
4. A method of claim 1 wherein the mood of the patient is improved.
- 10 5. A method of claim 1 wherein the energy level, mood and sleep quality of the patient are improved.
6. A method of claim 1 wherein the cognitive status of the patient is improved.
7. A method of claim 1 wherein the mental acuity of the patient is improved.
- 15 8. A method of claim 1 wherein the ability of the patient to perform in the workplace is improved.
9. A method of claim 1 wherein the health-related quality of life of the patient is improved.
- 20 10. A method of claim 1 wherein the social isolation of the patient is reduced.
11. A method of claim 1 wherein the functional independence of the patient is preserved.
12. A method of claim 1 wherein the patient is a human.
- 25 13. A method of claim 12 wherein the human is an elderly or chronically ill individual.
14. A method of claim 12 wherein the human has age-related decline in physical performance or is growth hormone deficient.
15. A method of claim 1 wherein the growth hormone secretagogue is an orally active growth hormone secretagogue.
- 30 16. A method of claim 15 wherein the growth hormone secretagogue is orally administered.
17. A method of claim 1 wherein the growth hormone secretagogue is a non-peptidyl growth hormone secretagogue.

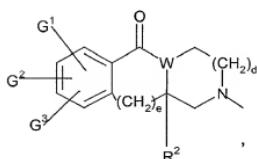
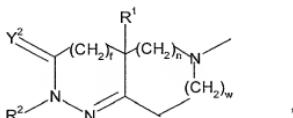
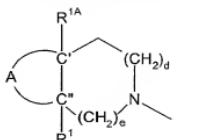
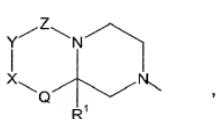
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18. A method of claim 1 wherein said growth hormone secretagogue is a compound of the Formula I:

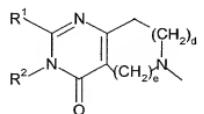


- 5 or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug, or a tautomer thereof, wherein:

10 HET is a heterocyclic moiety selected from the group consisting of



and



d is 0, 1 or 2:

e is 1 or 2.

f is 0 or 1;

- 15 n and w are 0, 1 or 2, provided that n and w cannot both be 0 at the same time;
 Y^2 is oxygen or sulfur;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C' and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

- NR²-C(O)-NR²-, -NR²-S(O)₂-NR²-, -O-C(O)-NR²-, -NR²-C(O)-O-, -C(O)-NR²-C(O)-,
 - 5 -C(O)-NR²-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-NR²-C(O)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-,
 - S(O)₂-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-O-C(O)-, -C(R⁹R¹⁰)-O-C(R⁹R¹⁰)-,
 - NR²-C(O)-C(R⁹R¹⁰)-, -O-C(O)-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-C(O)-NR²,
 - C(R⁹R¹⁰)-C(O)-O-, -C(O)-NR²-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(O)-O-C(R⁹R¹⁰)-,
 - C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -S(O)₂-NR²-C(R⁹R¹⁰)-C(R⁹R¹⁰)-,
 - 10 -C(R⁹R¹⁰)-C(R⁹R¹⁰)-NR²-C(O)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-O-C(O)-,
 - NR²-C(O)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -NR²-S(O)₂-C(R⁹R¹⁰)-C(R⁹R¹⁰)-,
 - O-C(O)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(O)-NR²,
 - C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(O)-, -C(R⁹R¹⁰)-NR²-C(O)-O-, -C(R⁹R¹⁰)-O-C(O)-NR²,
 - C(R⁹R¹⁰)-NR²-C(O)-NR²-, -NR²-C(O)-O-C(R⁹R¹⁰)-, -NR²-C(O)-NR²-C(R⁹R¹⁰)-,
 - 15 -NR²-S(O)₂-NR²-C(R⁹R¹⁰)-, -O-C(O)-NR²-C(R⁹R¹⁰)-, -C(O)-N=C(R¹¹)-NR²,
 - C(O)-NR²-C(R¹¹)=N-, -C(R⁹R¹⁰)-NR¹²-C(R⁹R¹⁰)-, -NR¹²-C(R⁹R¹⁰)-,
 - NR¹²-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(O)-O-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -NR²-C(R¹¹)=N-C(O)-,
 - C(R⁹R¹⁰)-C(R⁹R¹⁰)-N(R¹²)-, -C(R⁹R¹⁰)-NR¹²-, -N=C(R¹¹)-NR²-C(O)-,
 - C(R⁹R¹⁰)-C(R⁹R¹⁰)-NR²-S(O)₂-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-S(O)₂-NR²,
 - 20 -C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(O)-O-, -C(R⁹R¹⁰)-S(O)₂-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-S(O)₂-,
 - O-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-O-, -C(R⁹R¹⁰)-C(O)-C(R⁹R¹⁰)-,
 - C(O)-C(R⁹R¹⁰)-C(R⁹R¹⁰)- and -C(R⁹R¹⁰)-NR²-S(O)₂-NR²;
- Q is a covalent bond or CH₂;
- W is CH or N;
- 25 X is CR⁹R¹⁰, C=CH₂ or C=O;
- Y is CR⁹R¹⁰, O or NR²;
- Z is C=O, C=S or S(O)₂;
- G¹ is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, -CONH₂, -(C₁-C₄)alkyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, -(C₁-C₄)alkoxy optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, -(C₁-C₄)alkylthio, phenoxy, -COO(C₁-C₄)alkyl, N,N-di-(C₁-C₄)alkylamino, -(C₂-C₆)alkenyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, -(C₂-C₆)alkynyl optionally

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- independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_3\text{-}C_6)\text{cycloalkyl}$ optionally independently substituted with one or more $(C_1\text{-}C_4)\text{alkyl}$ groups, one or more halogens or one or more hydroxy groups, $-(C_1\text{-}C_4)\text{alkylamino carbonyl}$ or $\text{di-}(C_1\text{-}C_4)\text{alkylamino carbonyl}$;
- 5 G^2 and G^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, $-(C_1\text{-}C_4)\text{alkyl}$ optionally independently substituted with one to three halo groups and $-(C_1\text{-}C_4)\text{alkoxy}$ optionally independently substituted with one to three halo groups;
- R^1 is hydrogen, $-\text{CN}$, $-(\text{CH}_2)_q\text{N}(X^6)\text{C(O)X}^6$, $-(\text{CH}_2)_q\text{N(X}^6)\text{C(O)(CH}_2)_t\text{A}^1$,
- 10 $-(\text{CH}_2)_q\text{N(X}^6)\text{S(O)}_2(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{N(X}^6)\text{S(O)}_2\text{X}^6$, $-(\text{CH}_2)_q\text{N(X}^6)\text{C(O)N(X}^6)(\text{CH}_2)_t\text{A}^1$,
 $-(\text{CH}_2)_q\text{N(X}^6)\text{C(O)N(X}^6)(X^6)$, $-(\text{CH}_2)_q\text{C(O)N(X}^6)(\text{CH}_2)_t\text{A}^1$,
 $-(\text{CH}_2)_q\text{C(O)OX}^6$, $-(\text{CH}_2)_q\text{C(O)O(CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{OX}^6$, $-(\text{CH}_2)_q\text{OC(O)X}^6$,
 $-(\text{CH}_2)_q\text{OC(O)CH}_2\text{-A}^1$, $-(\text{CH}_2)_q\text{OC(O)N(X}^6)(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{OC(O)N(X}^6)(X^6)$,
 $-(\text{CH}_2)_q\text{C(O)X}^6$, $-(\text{CH}_2)_q\text{C(O)CH}_2\text{-A}^1$, $-(\text{CH}_2)_q\text{N(X}^6)\text{C(O)OX}^6$,
- 15 $-(\text{CH}_2)_q\text{N(X}^6)\text{S(O)}_2\text{N(X}^6)(X^6)$, $-(\text{CH}_2)_q\text{S(O)}_m\text{X}^6$, $-(\text{CH}_2)_q\text{S(O)}_m(\text{CH}_2)_t\text{A}^1$,
 $-(C_1\text{-}C_{10})\text{alkyl}$, $-(\text{CH}_2)_q\text{-A}^1$, $-(\text{CH}_2)_q\text{-(C}_3\text{-C}_7)\text{cycloalkyl}$, $-(\text{CH}_2)_q\text{Y}^1\text{-(C}_1\text{-C}_6)\text{alkyl}$,
 $-(\text{CH}_2)_q\text{Y}^1\text{-(CH}_2)_t\text{A}^1$ or $-(\text{CH}_2)_q\text{Y}^1\text{-(CH}_2)_t\text{-(C}_3\text{-C}_7)\text{cycloalkyl}$;
- where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1\text{-}C_4)\text{alkyl}$, hydroxy, $(C_1\text{-}C_4)\text{alkoxy}$, carboxyl, $-\text{CONH}_2$,
- 20 $-\text{S(O)}_m(C_1\text{-}C_6)\text{alkyl}$, $-\text{CO}_2(C_1\text{-}C_4)\text{alkyl ester}$, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;
- Y^1 is O, $\text{S(O)}_m\text{-C(O)NX}^6$, $-\text{CH=CH-}$, $-\text{C=C-}$, $-\text{N(X}^6)\text{C(O)-}$, $-\text{C(O)NX}^6$,
 $-\text{C(O)O-}$, $-\text{OC(O)N(X}^6)$ - or $-\text{OC(O)-}$;
- q is 0, 1, 2, 3 or 4;
- 25 t is 0, 1, 2 or 3;
 said $(\text{CH}_2)_q$ group and $(\text{CH}_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, $(C_1\text{-}C_4)\text{alkoxy}$, carboxyl, $-\text{CONH}_2$,
 $-\text{S(O)}_m(C_1\text{-}C_6)\text{alkyl}$, $-\text{CO}_2(C_1\text{-}C_4)\text{alkyl ester}$, 1H-tetrazol-5-yl , 1, 2 or 3 fluoro groups or 1 or 2 $(C_1\text{-}C_4)\text{alkyl}$ groups;
- 30 R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, $(C_1\text{-}C_6)\text{alkyl}$, $\text{phenyl}(C_1\text{-}C_3)\text{alkyl}$, $\text{pyridyl}(C_1\text{-}C_3)\text{alkyl}$, $\text{thiazolyl}(C_1\text{-}C_3)\text{alkyl}$ and $\text{thienyl}(C_1\text{-}C_3)\text{alkyl}$, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C^6 ,
 R^2 is hydrogen, $(C_1\text{-}C_6)\text{alkyl}$, $-(C_0\text{-}C_3)\text{alkyl-(C}_3\text{-C}_8)\text{cycloalkyl}$, $-(C_1\text{-}C_4)\text{alkyl-A}^1$ or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxy, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶), -S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 independently selected halo groups;

- 5 R³ is selected from the group consisting of A¹, (C₁-C₁₀)alkyl, -(C₁-C₆)alkyl-A¹, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl, -(C₁-C₅)alkyl-X¹-(C₀-C₅)alkyl-A¹ and -(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl-(C₃-C₇)cycloalkyl;

where the alkyl groups in the definition of R³ are optionally substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1, 2, 3, 4 or 5 independently selected halo

- 10 groups or 1, 2 or 3 independently selected -OX³ groups;

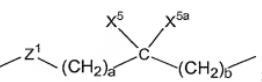
X¹ is O, S(O)_m, -N(X²)C(O)-, -C(O)N(X²)-, -OC(O)-, -C(O)O-, -CX²=CX²-, -N(X²)C(O)O-, -OC(O)N(X²)- or -C≡C-;

R⁴ is hydrogen, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl, or R⁴ is taken together with R³ and the carbon atom to which they are attached and form (C₅-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl,

- 15 a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4

- 20 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five to seven membered ring;

- 25 R⁶ is a bond or is ;

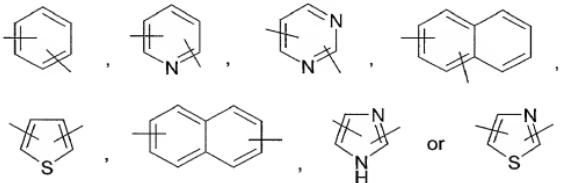
where a and b are each independently 0, 1, 2 or 3;

X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, CF₃, A¹ and optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is

- 30 optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

- or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;
- 5 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;
- 10 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;
- 15 Z^1 is a bond, O or N-X², provided that when a and b are both 0 then Z^1 is not N-X² or O;
- 20 or R^6 is -(CR^aR^b)_a-E-(CR^aR^b)_b-, where the -(CR^aR^b)_a- group is attached to the carbonyl carbon of the amide group of the compound of formula I and the -(CR^aR^b)_b group is attached to the terminal nitrogen atom of the compound of formula I;
- 25 E is -O-, -S-, -CH=CH- or an aromatic moiety selected from



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said aromatic moiety in the definition of E optionally substituted with up to three halo, hydroxy, -N(R^c)(R^c), (C₁-C₆)alkyl or (C₁-C₆)alkoxy;

R^a and R^b are, for each occurrence, independently hydrogen, (C₁-C₆)alkyl, trifluoromethyl, phenyl or monosubstituted (C₁-C₆)alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^c, S(O)_mR^c, C(O)OR^c, (C₃-C₇)cycloalkyl, -N(R^c)(R^c), -C(O)N(R^c)(R^c), or R^a or R^b may independently be joined to one or both of R⁷ or E (where E is other than O, S or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^a or R^b and the R⁷ or E group, wherein the bridge contains 1 to 8 carbon atoms; or R^a and R^b may be joined to one another to form a (C₃-C₇)cycloalkyl;

R^c, for each occurrence, is independently hydrogen or (C₁-C₆)alkyl; a and b are independently 0, 1, 2 or 3, with the proviso that if E is -O- or -S-, b is other than 0 or 1 and with the further proviso that if E is -CH=CH-, b is other than 0;

R⁷ and R⁸ are each independently hydrogen or optionally substituted (C₁-C₆)alkyl; where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 -O-C(O)(C₁-C₁₀)alkyl groups or 1 to 3 (C₁-C₆)alkoxy groups; or R⁷ and R⁸ can be taken together to form -(CH₂)_n-L-(CH₂)_n-; where L is C(X²)(X²), S(O)_m or N(X²);

R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, fluoro, hydroxy and (C₁-C₅)alkyl optionally independently substituted with 1-5 halo groups;

R¹¹ is selected from the group consisting of (C₁-C₅)alkyl and phenyl optionally substituted with 1-3 substituents each independently selected from the group consisting of (C₁-C₅)alkyl, halo and (C₁-C₅)alkoxy;

R¹² is selected from the group consisting of (C₁-C₅)alkylsulfonyl, (C₁-C₅)alkanoyl and (C₁-C₅)alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A¹ for each occurrence is independently selected from the group consisting of (C₅-C₇)cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4-to 8-membered ring optionally having 1 to 4 heteroatoms independently selected

from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, 5 fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

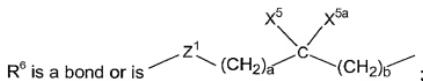
- A¹ for each occurrence is independently optionally substituted, on one or 10 optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶, -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl, -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -S(O)₂N(X⁶)(X⁶), 15 -N(X⁶)S(O)₂-phenyl, -N(X⁶)S(O)₂X⁶, -CONX¹¹X¹², -S(O)₂NX¹¹X¹², -NX⁶S(O)₂X¹², -NX⁶CONX¹¹X¹², -NX⁶S(O)₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy; 20 where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl; the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 (C₁-C₁₀)alkanoyloxy groups or 1 to 3 (C₁-C₆)alkoxy groups; 25 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thieryl, provided that when X¹² is not hydrogen, the X¹² group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃; 30 or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r-; L¹ is C(X²)(X²), O, S(O)_m or N(X²); r for each occurrence is independently 1, 2 or 3; X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted

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- (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halo groups or 1-3 OX³ groups;
- X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;
- 5 X⁶ for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenated cycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently mono- or di-substituted with (C₁-C₄)alkyl, hydroxy, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester or 1H-tetrazol-5-yl; or
- 10 when there are two X⁶ groups on one atom and both X⁶ are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the two X⁶ groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷ as a ring member;
- 15 X⁷ is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxy;
- m for each occurrence is independently 0, 1 or 2;
- with the provisos that:
- 1) X⁶ and X¹² cannot be hydrogen when attached to C(O) or S(O)₂ in the form C(O)X⁶, C(O)X¹², S(O)₂X⁶ or S(O)₂X¹²; and
- 20 2) when R⁶ is a bond then L is N(X²) and each r in the definition -(CH₂)_r-L-(CH₂)_r is independently 2 or 3.
19. A method of claim 18 wherein the growth hormone secretagogue is a compound of Formula I-A
-
- I-A
- 25 a racemic-diastereomeric mixture or an optical isomer of said compound or a pharmaceutically-acceptable salt or a prodrug thereof, or a tautomer thereof,
wherein
- f is 0;
- n is 0 and w is 2, or n is 1 and w is 1, or n is 2 and w is 0;
- 30 Y is oxygen or sulfur;

- R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOC(O)X⁶, -(CH₂)_qOC(O)N(X⁶)(X⁶),
- 5 -(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶, -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹, -(C₁-C₁₀)alkyl, -(CH₂)_q-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl, -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;
- 10 where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;
- Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;
- 15 q is 0, 1, 2, 3 or 4;
- t is 0, 1, 2 or 3;
- said (CH₂)_q group and (CH₂)_t group may each be optionally substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl,
- 20 -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C₁-C₄)alkyl;
- R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹; where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶), -S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 halogen;
- 25 R³ is A¹, (C₁-C₁₀)alkyl, -(C₁-C₆)alkyl-A¹, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl, -(C₁-C₅)alkyl-X¹-(C₀-C₅)alkyl-A¹ or -(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl-(C₃-C₇)cycloalkyl;
- 30 where the alkyl groups in the definition of R³ are optionally substituted with, -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX³; X¹ is O, S(O)_m, -N(X²)C(O)-, -C(O)N(X²)-, -OC(O)-, -C(O)O-, -CX²=CX²- , -N(X²)C(O)O-, -OC(O)N(X²)- or -C≡C-;
- R⁴ is hydrogen, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;

X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five to seven membered ring;



- 5 where a and b are independently 0, 1, 2 or 3;
X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;
the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);
- 10 R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;
where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C₁-C₁₀)alkyl or 1 to 3 (C₁-C₆)alkoxy; or
- 15 R⁷ and R⁸ can be taken together to form -(CH₂)_rL-(CH₂)_r;
where L is C(X²)(X²), S(O)_m or N(X²);
- A¹ in the definition of R¹ is a partially saturated, fully saturated or fully unsaturated
- 20 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4
- 25 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;
- A¹ in the definition of R², R³, R⁶, R⁷ and R⁸ is independently (C₅-C₇)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-

membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

- 5 and oxygen;

10 A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶, -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl, -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶), -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl or tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

15 where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl; the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

20 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thieryl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃; or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

25 where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

30 X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

- X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;
X⁶ is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally
5 substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or
when there are two X⁶ groups on one atom and both X⁶ are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the
10 atom to which the two X⁶ groups are attached, form a 4- to 9- membered ring
optionally having oxygen, sulfur or NX⁷;

- X⁷ is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and
m for each occurrence is independently 0, 1 or 2;
with the proviso that:
15 X⁶ and X¹² cannot be hydrogen when it is attached to C(O) or SO₂ in the form
C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹², and
when R⁶ is a bond then L is N(X²) and each r in the definition -(CH₂)_r-L-(CH₂)_r- is
independently 2 or 3.
20. A method of claim 19 wherein the growth hormone secretagogue is
21. 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, a prodrug thereof
22. or a pharmaceutically acceptable salt of said growth hormone secretagogue or said
prodrug.
23. A method of claim 20 wherein the growth hormone secretagogue is
24. 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, L-tartrate.
25. A method of claim 19 wherein the growth hormone secretagogue is
26. 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-yl)methyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl]-2-methyl-propionamide, a prodrug thereof or a pharmaceutically
30. acceptable salt of said growth hormone secretagogue or said prodrug.
27. A method of claim 22 wherein the growth hormone secretagogue is
the (L)-(+) -tartaric acid salt of 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-

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oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide.

24. A method of claim 18 wherein the growth hormone secretagogue is 2-amino-N-(1(R)-benzyloxymethyl-2-[1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl)-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said growth hormone secretagogue or said prodrug.

25. A method of claim 24 wherein the growth hormone secretagogue is the (L)-(+)-tartaric acid salt of 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl)-2-methyl-propionamide.

26. A method of claim 1 which further comprises administering recombinant growth hormone or a growth hormone secretagogue selected from the group consisting of GHRP-6, GHRP-1, GHRP-2, hexarelin, growth hormone releasing factor, an analog of growth hormone releasing factor, IGF-I and IGF-II.

27. A method of claim 1 which further comprises administering an antidepressant, a prodrug thereof or a pharmaceutically acceptable salt of said antidepressant or said prodrug.

28. A method of claim 27 wherein said antidepressant is a norepinephrine reuptake inhibitor (NERI), selective serotonin reuptake inhibitor (SSRI), monoamine oxidase inhibitor (MAO), combined NERI/SSRI, or an atypical antidepressant, a prodrug of said antidepressant or a pharmaceutically acceptable salt of said antidepressant or said prodrug.

29. A method of claim 28 wherein said antidepressant is a selective serotonin reuptake inhibitor (SSRI), a prodrug thereof or a pharmaceutically acceptable salt of said SSRI or said prodrug.

30. A method of claim 29 wherein said SSRI is citalopram, femoxetine, fluoxetine, fluvoxamine, indalpine, indeloxazine, milnacipran, paroxetine, sertraline, sibutramine or zimeldine, a prodrug of said SSRI or a pharmaceutically acceptable salt of said SSRI or said prodrug.

31. A method of claim 30 wherein said SSRI is sertraline, a prodrug thereof or a pharmaceutically acceptable salt of sertraline or said prodrug.

32. A method of claim 31 wherein said SSRI is sertraline hydrochloride.

33. A method of claim 1 which further comprises administering an antipsychotic agent, a prodrug thereof or a pharmaceutically acceptable salt of said antipsychotic agent or said prodrug.

34. A method of claim 33 wherein the antipsychotic agent is
5 chlorpromazine, haloperidol, clozapine, loxapine, molindone hydrochloride,
thiothixene, olanzapine, ziprasidone hydrochloride, prochlorperazine, perphenazine,
trifluoperazine hydrochloride or risperidone.

35. A method of claim 1 which further comprises administering an
antianxiety agent, a prodrug thereof or a pharmaceutically acceptable salt of said
10 antianxiety agent or said prodrug.

36. A method of claim 35 wherein the antianxiety agent is alprazolam,
clonazepam, lorazepam, oxazepam, chlordiazepoxide hydrochloride, diazepam,
buspirone hydrochloride, doxepin hydrochloride, hydroxyzine pamoate or
clonazepam.

15 37. A method of claim 1 which further comprises administering a
naturaceutic, a prodrug thereof or a pharmaceutically acceptable salt of said
naturaceutic or said prodrug.

38. A method of claim 37 wherein the naturaceutic is ginko biloba, St.
John's Wart, valerian or melatonin.

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